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FURTHER OBSERVATIONS ON THE SPECIFICITY OF HYPOXANTHINE FOR PHYCOMYCES

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In a previous communication Robbins and Kavanagh[1] reported hypoxanthine to benefit the spore germination and early mycelial growth of *Phycomyces* in a basal mineral-dextrose solution containing asparagine and thiamine. The benefit was more marked in the presence of the filtrate from a potato extract (D_R fraction) which had been treated with charcoal. A comparison of the activity of hypoxanthine with other compounds led to the conclusion that the active substance must have the eighth position and the seventh or ninth position on the purine ring open for substitution, oxygen in the sixth position and hydrogen or NH_2 in the second position.

Through the courtesy of Dr. George Hitchings I have been able to test 5 additional compounds. These were 8-oxypurine, 6-amino-8-oxypurine, 6,8-dioxypurine, 7-methyl guanine and 1,7-dimethyl guanine. The effect of each of these compounds on the percentage of *Phycomyces* spores which germinated at 25°C. on a mineral-dextrose medium containing thiamine, asparagine and one per cent purified agar was compared with that of hypoxanthine and guanine. Each compound was used alone and in the presence of a D_R fraction prepared from potato tubers. A comparison was made also between the action of hypoxanthine, of guanine and of each of the five analogs on the dry weight of the mycelium produced in 48 hours at 27°C. in 10 ml. of the basal liquid medium and the same medium to which the D_R fraction was added. Each compound was used per flask or per petri dish in the following amounts: 100 μg., 10 μg., 1 μg and 0.1 μg.

The 8-oxypurine, 6-amino-8-oxypurine and 6,8-dioxypurine were ineffective. Although identical otherwise with hypoxanthine the 8-oxypurine has hydrogen in the 6th position and the 6-amino-8-oxypurine has the amino group in the 6th position. The inactivity of these two compounds agrees with the earlier observations which indicated that the active compound should contain oxygen in the 6th position. The 6,8-dioxy-

purine is identical with hypoxanthine except that the hydrogen in the 8th position in hypoxanthine is replaced by oxygen. This change rendered the 6,8-dioxypurine inactive; a result which agrees with the earlier conclusion by Robbins and Kavanagh that the 8th position must be opened for possible substitution.

It was anticipated that the two guanines also might prove to be inactive since both had the CH_3 group in the 7th position and the previous results indicated that in order to have an active compound the 7th or 9th position should be open for substitution. However, both the 7-methyl guanine and the 1,7-dimethyl guanine proved to be partially active. It is not possible to determine relative activities accurately with the methods used. It appeared, however, that the 7-methyl guanine and 1,7-dimethyl guanine had between 1/10 and 1/100 the activity of hypoxanthine.

These results support the idea that the action of hypoxanthine on *Phycomyces* has a considerable degree of specificity. Guanine is the only other compound[2] which has been found to approach the activity of hypoxanthine.

Pennington[3] reported hypoxanthine or an equimolecular mixture of adenine and guanine to be essential for the growth of *Spirillum serpens*. Neither adenine nor guanine alone was effective and sufficient amounts of either interfered with the physiological effectiveness of hypoxanthine.

An increasing number of observations on various organisms[4] show that the purines probably function as growth substances. There seems, however, to be little uniformity since the specific purines which are active appear to vary from organism to organism.

[1] Robbins, W. J., and Kavanagh, F., *Proc. Nat. Acad. Sci.*, **28**, 65–69 (1942).

[2] W. J. Robbins and F. Kavanagh found a purine, kindly furnished by Dr. D. W. Wooley, to have about one-half the activity of hypoxanthine. This compound is aspurine and is not fully defined chemically. See Wooley, D. W., *16th International Physiological Congress, Proc. II*, 126 (1938). The formula given is $C_4H_7N_5O_2$. The picrate was found to be similar in all of its physical properties to the picrate of adenine. We prepared the silver nitrate crystals of aspurine and found them to be very small, isolated and not in clusters, nearly straight and pointed. The silver nitrate crystals of aspurine treated with nitrous acid were identical in appearance with the silver nitrate crystals of hypoxanthine.

[3] Pennington, D. E., *Proc. Nat. Acad. Sci.*, **28**, 272–276 (1942).

[4] For references to earlier work, see the papers by Robbins and Kavanagh and by Pennington.

A MUTANT OF DROSOPHILA MELANOGASTER RESEMBLING THE SO-CALLED UNSTABLE GENES OF DROSOPHILA VIRILIS

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In a number of papers Demerec (see 1941) described genetic phenomena in *Drosophila virilis* which he interprets as due to unstable, ever-mutating genes. The best analyzed case is that of alleles at the miniature (small wings) locus. The decisive facts are: Among a series of *mt*-alleles two called 3 and 5 showed the phenomenon in question. This means that the offspring consists of *mt* individuals, mosaics and normals, the latter breeding true, the others not. A mosaic is a fly with more or less miniature patches on normal wings, or one normal and one miniature wing (see below). Unstable *mt* appears in three well-defined "sub-alleles." Of these, mt^b is stable, mt^c produces only miniature and mosaic offspring, and mt^a normal, miniature and mosaic offspring. Demerec considers these facts the consequence of, in mt^a, instability of the *mt* gene both in somatic and germinal cells and, in mt^c, of instability only in somatic cells. From the size of the mosaic spots and the number of wild-type flies, it is concluded that the "mutability" begins rather late in development and the mutation is always one from miniature to normal, both in somatic and sex cells. In addition, a series of modifiers exist. One increases the number of normals (called germinal mutability) but only in the mt^a line, which always segregates normals. Another series of modifiers (called *S*-genes) increases only the mosaic spots (i.e., are supposed to act only upon somatic mutability). Without these enhancers a small percentage of flies show mosaic spots and these extend rarely to an entire wing. In the presence of the modifiers the percentage of mosaics is increased up to 95 per cent, and one of the *S*-genes frequently produces flies with one normal and one miniature or mosaic wing. There is, in addition, a sexual difference in all these effects. Finally, the *a*, *b*, *c* forms may change into each other and in a reversible way.

I had always expected that these important facts would, one day, find their explanation without recourse to "unstable genes." The case discovered in *Drosophila melanogaster* seems to furnish such an explanation. In the course of a study of spontaneous mutation (soon to be presented in detail) a number of alleles were found at the silver (1st chromosome) and arc (2d chromosome) loci. The silver alleles produce predominantly pointed wings and are therefore called svr^{poi}, $svr^{poi\,s}$, etc. The arc alleles are expressed, if at all, as broad and angular wings called *bran*, *bran'*, $bran^{d\phi}$, etc. These two loci have, in addition, a typical interaction which characterizes the different combinations of the alleles at the two loci and

some alleles can be distinguished only by this combination effect in which either the bran or the poi phenotype is more or less epistatic or a compromise form is produced. Thus *bran* homozygous with svr^{poi} has a soft, shortened, more or less pointed and blistered wing called soft blistered. Among these combinations one was found between svr^{poi} and a *bran* allele called $bran^{dp}$ which simulated completely the mt^c case in *Drosophila virilis*. The offspring in this line, i.e., $bran^{dp}/bran^{dp}$; svr^{poi}/svr^{poi} (or hemizygous male) consists of a majority of pointed flies, a minority of flies with one wing pointed, one wing truncated (abbreviated *poi dp*) and a percentage of transitions from a pointed to a truncated wing in all conditions of asymmetry down to a symmetrical, truncated (dumpy-like) wing. All types, if selected, produce the same offspring, but modifiers for higher percentages of the not pointed wings can be selected. The constitution of this line, i.e., homozygosity of the two loci is easily tested in outcrosses as well as with different alleles of the two loci. Whenever the parental combination is recovered, and also in a few compounds of $bran^{dp}$ with another *bran* allele, the characteristic variation of the phenotype appears. The homozygote $bran^{dp}/bran^{dp}$—and this is an important fact—has no visible effect if the svr^{poi} mutant is absent.

The first question is whether the series of phenotypes from pointed to dumpy, which we may call in brief the *poi dp* effect, can be assumed to be comparable to those described by Demerec. There is no doubt in regard to the unchanged wings, i.e., miniature in virilis, pointed in my case, nor for the type with one wing +, one *mt* in virilis, one pointed, one dumpy in my case. The decisive types are the mosaic types in virilis and the intermediates in my case. Demerec assumes that the mosaic spots of miniature cells are genetically miniature, and the normal wing parts are genetically normal by somatic mutation. If one thinks of such mosaics in a general way, comparing them with gynanders or mosaic spots analyzed by markers, one is led to such an interpretation. But in the case in question this is not conclusive. A miniature wing is essentially one in which cell growth after pupation is inhibited (see Dobzhansky, 1929; Goldschmidt, 1935; Waddington, 1940). If this inhibition had a narrow threshold condition so that it would act only partially in the presence of a certain genetic condition, a mosaic-like structure of the wing would appear in the varying and asymmetrical patches of miniature tissue, including also the normal and the +, *mt* wings. Actually we know of no case of a real mosaic within a wing, but many cases in which such an asymmetrical threshold effect occurs (see my discussion of the nicking effect, in Goldschmidt, 1940, p. 222 ff.). In my case the decision is between a pointed and a ± truncated wing. As truncation is a phenomenon at the wing edge, no mosaic in a plane can become visible. The mosaic produced by the transgressive threshold action appears in the form of a wing edge showing all transitions from pointed to dumpy,

more or less asymmetrically. Thus I believe that also in the miniature case there is no necessity for the assumption that the normal wing cells are genetically different from the miniature cells. A threshold condition acting within narrow limits can produce the apparent mosaic within the genetically miniature cells.

The data in my case indicate clearly the reason for the variable effect. The $bran^{dp}$ allele, interacting with the svr^{poi} locus, is responsible for the threshold condition. Other *bran* alleles have a truncating effect alone and together with svr^{poi} produce wing types like soft blistered, truncated blistered, rudimentary blistered, etc. But $bran^{dp}$ is an allele which alone has no visible effect but with svr^{poi} hardly succeeds in pushing the pointed wing over the threshold toward a dumpy wing. In other words, the *bran* allele acts near the level of epistasis between *bran* and pointed with the effect of a scintillating epistasis for whole wings or parts of them. In our case the explanation is clear: (1) a combination of two interacting loci, (2) the presence of one allele affecting epistasis near the threshold level; (3) the developmental physiology of the wing. As the parallelism with miniature is practically complete (including also modifiers and sexual difference), I conclude that mt^c collaborates with another allele which, like $bran^{dp}$, has no visible action alone, but, if epistatic, pushes wing cell development toward normal just as $bran^{dp}$ pushes it towards truncation, and, further, that mt^c is not an *mt* allele but ordinary *mt* in the presence of the other locus, say *e*, which has an epistatic action near the threshold, but no visible effect alone.

In my case the location of $bran^{dp}$ in the arc region is clear because alleles with visible action exist. In Demerec's case the second locus *e* is difficult to locate because it also had no action alone, and no alleles with visible effect have been reported. It might even be linked with the miniature locus, as suggested by some data. But there are no general difficulties to an understanding of mt^c without unstable genes. We turn now to mt^a. Here another group of facts found in my case comes in. It turned out that within the *poi dp* stock an allele of *bran* is present occasionally, called $bran^r$, which together with svr^{poi} produces a wing with a phenotype like rudimentary and blistered. This combination is less viable and, if produced by mating $bran^{dp}/bran^r$, appears in less than a quarter of the expected number. The allele $bran^r$ alone produces a kind of truncated wing. The segregating $bran^r/bran^r$; svr^{poi} flies breed true. Returning to our former comparison of the two cases, the svr^{poi} locus paralleled the *mt* locus in virilis; $bran^{dp}$ paralleled an unknown locus in virilis with the discussed effect upon epistasis, otherwise producing a normal wing. If we had now in addition another allele of the latter (called *e'*) which if homozygous produces complete epistasis of its normal effect over the *mt* effect, thus paralleling the action of $bran^r$, a true breeding normal fly would result from this combination *mt/mt; e'/e'*. A line containing *e* and *e'* with a chance for segregation

of e'/e' would be the complete explanation for Demerec's mt^a, throwing the "mutation" to normal. There is one detail, however, which cannot be explained as long as the detailed data on the virilis case are not available, namely, the normal constitution of the mt^a line in regard to e' and e. What I termed e' may be more than one locus with complicated segregation in addition to the possibility of linkage with mt. The results of outcrosses as well as the details of the so-called reversible changes of mt^a into b, c, and vice versa, ought to furnish this information. I do not doubt that a recheck of the facts, abandoning the idea of the unstable gene and trying to apply the interpretation of my so similar case would result in a simple explanation of all details in terms of factor interaction, epistasis and threshold conditions.

It would be interesting to try to apply this interpretation also to the cases of variegation in plants, though there is the basic difficulty that nothing is known of developmental genetics of color, which prevents a discussion of the possibility of a purely phenotypical threshold effect. The most interesting case of this kind is the one beautifully analyzed by Rhoades. Looking at his data I am struck again by the great parallelism to my case: A homozygous condition for colorless is made to produce mosaics by the recombination with another mutant Dt which alone has no visible effect at all. Thus we have the parallel: aa (colorless) parallels svr^{poi}, Dt parallels $bran^{dp}$. Rhoades himself emphasizes that up to this point unstable genes are not needed as an explanation. But he thinks to have proven his point by finding that from colored or mosaic anthers present in a stock made up by outcrossing, pollen may be derived which acts either as aa or as heterozygous for a and a color allele (A). This again parallels completely my case when the allele $bran^r$ is present which then, here, would be represented by a new Dt allele which produces color with the tester allele of a and which seems to have been introduced when making up the stock with spotted anthers which required a special constitution. The parallel is so close that a test may be suggested which should be easy to perform in the maize stock of Rhoades. In the published account I cannot find results which exclude such an interpretation, but the decisive tests would still have to be made, e.g., numerous crosses with the tester stock and pollen from green anthers in the mosaic stock which gave the "mutants" from colored anthers.

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A TABLE DETERMINING L.D.50 OR THE FIFTY PER CENT END-POINT

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It has been shown[1] that if we may use the growth curve in bio-assay and if we have three proportions P_1, P_2, P_3 of the population affected by doses D, Dr, Dr^2 of some biological, the values of the parameters γ and α of the curve may be obtained in terms of the two simple combinations

$$A = 2(P_1 + P_2 + P_3) - 3 \qquad \text{and } B = P_3 - P_1 \tag{1}$$

of these proportions provided the number n of animals used at each dosage be the same. It is therefore possible to give a double entry table which states the values of "γ" $= \gamma/c$ and of "α" $= c\alpha$, where $c = \log r$, and of their standard deviations as computed by the formulae of R. A. Fisher[2] for $n = 1$: to obtain the standard deviations for any value of n it is merely necessary to divide their tabulated values by $\sqrt{n}$.

In the table the values of B go by intervals of 0.05 from 0.30 to 0.95, inclusive. Because the standard deviations of γ are large for small values of B, the table is not carried below $B = 0.30$. The values of A are given by intervals 0.1 from 0 to the highest value possible for the given values of B, which ranges from $A = 1.0$ for $B = 0.95$ to $A = 2.3$ for $B = 0.30$. If n is 20 or any divisor thereof the values of "γ" and "α" and their standard deviations (for $n = 1$) can be read directly from the table; for other values of n, interpolation is necessary. The table is restricted to positive values of A and B; for negative values of either or both, the numerical values of "γ" and "α" will be in the table but signs of "γ" or "α" or both will have to be taken in accordance with this scheme:

	$A > 0$	$A < 0$
$B > 0$	γ neg., α pos.	γ pos., α pos.
$B < 0$	γ pos., α neg.	γ neg., α neg.

Bacteriologists will prefer to work in terms of dilutions $1:a$, $1:ar$, $1:ar^2$ rather than dosages. Dilutions and dosages are reciprocals, which means that as logarithms are used each is the negative of the other. To use the table to obtain that dilution $1:\delta$ which for the amount of the biological administered affects half the population one has merely to take

$$\log \delta = \log ar - \text{"}\gamma\text{"} \log r \pm \sigma(\text{"}\gamma\text{"}) \log r \tag{2}$$

and convert to antilogarithms. This can be illustrated on an example more clearly than stated in words.

VALUES FOR "γ" = γ/c AND "α" = $c\alpha$ FOR SPECIFIED VALUES OF A AND B AND FOR THEIR STANDARD DEVIATIONS IF $n = 1$

A	B	0.65	0.70	0.75	0.80	0.85	0.90	0.95
0	"γ"	0 ± 0.88	0 ± 0.81	0 ± 0.75	0 ± 0.69	0 ± 0.64	0 ± 0.58	0 ± 0.50
	"α"	0.78 ± 0.93	0.87 ± 0.99	0.97 ± 1.07	1.10 ± 1.18	1.26 ± 1.35	1.47 ± 1.62	1.83 ± 2.26
0.1	"γ"	−0.06 ± 0.88	−0.06 ± 0.81	−0.05 ± 0.75	−0.05 ± 0.69	−0.05 ± 0.64	−0.05 ± 0.58	−0.05 ± 0.50
	"α"	0.78 ± 0.93	0.87 ± 0.99	0.98 ± 1.07	1.10 ± 1.18	1.26 ± 1.36	1.48 ± 1.63	1.84 ± 2.27
0.2	"γ"	−0.12 ± 0.88	−0.11 ± 0.81	−0.11 ± 0.75	−0.11 ± 0.69	−0.10 ± 0.64	−0.10 ± 0.58	−0.09 ± 0.50
	"α"	0.78 ± 0.94	0.87 ± 1.00	0.98 ± 1.08	1.11 ± 1.19	1.27 ± 1.37	1.49 ± 1.64	1.86 ± 2.29
0.3	"γ"	−0.18 ± 0.87	−0.17 ± 0.81	−0.16 ± 0.74	−0.16 ± 0.69	−0.15 ± 0.63	−0.15 ± 0.57	−0.14 ± 0.50
	"α"	0.79 ± 0.94	0.88 ± 1.01	0.99 ± 1.09	1.12 ± 1.20	1.29 ± 1.39	1.51 ± 1.66	1.89 ± 2.31
0.4	"γ"	−0.24 ± 0.87	−0.23 ± 0.80	−0.22 ± 0.74	−0.21 ± 0.68	−0.20 ± 0.63	−0.20 ± 0.57	−0.18 ± 0.50
	"α"	0.80 ± 0.96	0.90 ± 1.02	1.01 ± 1.11	1.14 ± 1.23	1.32 ± 1.41	1.55 ± 1.70	1.94 ± 2.35
0.5	"γ"	−0.29 ± 0.87	−0.28 ± 0.80	−0.27 ± 0.73	−0.26 ± 0.68	−0.25 ± 0.62	−0.24 ± 0.57	−0.23 ± 0.50
	"α"	0.81 ± 0.97	0.91 ± 1.04	1.03 ± 1.13	1.17 ± 1.25	1.36 ± 1.45	1.60 ± 1.74	2.01 ± 2.40
0.6	"γ"	−0.35 ± 0.86	−0.34 ± 0.79	−0.32 ± 0.72	−0.31 ± 0.67	−0.30 ± 0.61	−0.29 ± 0.56	−0.27 ± 0.51
	"α"	0.83 ± 0.99	0.94 ± 1.06	1.06 ± 1.16	1.21 ± 1.29	1.40 ± 1.50	1.67 ± 1.80	2.10 ± 2.46
0.7	"γ"	−0.41 ± 0.86	−0.39 ± 0.78	−0.37 ± 0.71	−0.36 ± 0.66	−0.35 ± 0.60	−0.34 ± 0.55	−0.32 ± 0.52
	"α"	0.85 ± 1.01	0.96 ± 1.09	1.09 ± 1.20	1.26 ± 1.34	1.46 ± 1.55	1.75 ± 1.86	2.22 ± 2.53
0.8	"γ"	−0.46 ± 0.84	−0.44 ± 0.77	−0.42 ± 0.70	−0.41 ± 0.64	−0.40 ± 0.59	−0.39 ± 0.55	−0.37 ± 0.52
	"α"	0.88 ± 1.04	1.00 ± 1.13	1.14 ± 1.25	1.31 ± 1.40	1.55 ± 1.63	1.86 ± 1.96	2.37 ± 2.63
0.9	"γ"	−0.51 ± 0.83	−0.49 ± 0.75	−0.47 ± 0.68	−0.46 ± 0.62	−0.45 ± 0.58	−0.44 ± 0.54	−0.43 ± 0.53
	"α"	0.91 ± 1.08	1.04 ± 1.18	1.20 ± 1.31	1.39 ± 1.49	1.65 ± 1.73	2.01 ± 2.10	2.58 ± 2.80
1.0	"γ"	−0.56 ± 0.81	−0.54 ± 0.73	−0.52 ± 0.66	−0.51 ± 0.60	−0.51 ± 0.56	−0.50 ± 0.53	−0.50 ± 0.55
	"α"	0.96 ± 1.13	1.10 ± 1.24	1.27 ± 1.39	1.49 ± 1.59	1.80 ± 1.88	2.22 ± 2.30	2.95 ± 3.23
1.1	"γ"	−0.61 ± 0.79	−0.59 ± 0.71	−0.57 ± 0.63	−0.56 ± 0.58	−0.56 ± 0.54	−0.57 ± 0.53	
	"α"	1.01 ± 1.20	1.17 ± 1.33	1.37 ± 1.50	1.63 ± 1.75	2.00 ± 2.12	2.58 ± 2.81	
1.2	"γ"	−0.66 ± 0.76	−0.63 ± 0.67	−0.62 ± 0.60	−0.62 ± 0.55	−0.63 ± 0.52		
	"α"	1.08 ± 1.28	1.26 ± 1.44	1.51 ± 1.67	1.83 ± 2.00	2.35 ± 2.65		
1.3	"γ"	−0.70 ± 0.72	−0.68 ± 0.63	−0.67 ± 0.56	−0.68 ± 0.52			
	"α"	1.17 ± 1.39	1.39 ± 1.61	1.70 ± 1.92	2.18 ± 2.57			

VALUES FOR "γ" = γ/c AND "α" = $c\alpha$ FOR SPECIFIED VALUES OF A AND B AND FOR THEIR STANDARD DEVIATIONS IF $n = 1$

A		B = 0.65	0.70	0.75	0.80	0.85	0.90	0.95
1.4	"γ"	−0.74 ± 0.68	−0.73 ± 0.58	−0.73 ± 0.51				
	"α"	1.30 ± 1.56	1.58 ± 1.87	2.04 ± 2.51				
1.5	"γ"	−0.78 ± 0.61	−0.78 ± 0.52					
	"α"	1.48 ± 1.83	1.92 ± 2.47					
1.6	"γ"	−0.83 ± 0.53						
	"α"	1.81 ± 2.44						

A		B = 0.30	0.35	0.40	0.45	0.50	0.55	0.60
0	"γ"	0 ± 1.92	0 ± 1.65	0 ± 1.44	0 ± 1.28	0 ± 1.15	0 ± 1.05	0 ± 0.96
	"α"	0.31 ± 0.74	0.37 ± 0.76	0.42 ± 0.77	0.48 ± 0.79	0.55 ± 0.82	0.62 ± 0.84	0.69 ± 0.88
0.1	"γ"	−0.11 ± 1.94	−0.10 ± 1.66	−0.09 ± 1.44	−0.08 ± 1.28	−0.07 ± 1.15	−0.07 ± 1.05	−0.06 ± 0.96
	"α"	0.31 ± 0.74	0.37 ± 0.76	0.42 ± 0.77	0.48 ± 0.79	0.55 ± 0.82	0.62 ± 0.84	0.69 ± 0.88
0.2	"γ"	−0.23 ± 1.98	−0.20 ± 1.68	−0.18 ± 1.46	−0.16 ± 1.29	−0.15 ± 1.16	−0.13 ± 1.05	−0.13 ± 0.96
	"α"	0.31 ± 0.74	0.37 ± 0.76	0.43 ± 0.77	0.49 ± 0.79	0.55 ± 0.82	0.62 ± 0.85	0.70 ± 0.89
0.3	"γ"	−0.34 ± 2.04	−0.30 ± 1.71	−0.26 ± 1.48	−0.24 ± 1.30	−0.22 ± 1.16	−0.20 ± 1.05	−0.19 ± 0.96
	"α"	0.31 ± 0.75	0.37 ± 0.76	0.43 ± 0.78	0.49 ± 0.80	0.56 ± 0.82	0.63 ± 0.85	0.70 ± 0.90
0.4	"γ"	−0.45 ± 2.12	−0.39 ± 1.76	−0.35 ± 1.51	−0.31 ± 1.32	−0.29 ± 1.17	−0.27 ± 1.05	−0.25 ± 0.96
	"α"	0.32 ± 0.75	0.37 ± 0.76	0.43 ± 0.78	0.50 ± 0.80	0.56 ± 0.83	0.63 ± 0.86	0.71 ± 0.90
0.5	"γ"	−0.56 ± 2.22	−0.49 ± 1.82	−0.43 ± 1.54	−0.39 ± 1.34	−0.36 ± 1.18	−0.33 ± 1.06	−0.31 ± 0.95
	"α"	0.32 ± 0.76	0.38 ± 0.77	0.44 ± 0.79	0.50 ± 0.81	0.57 ± 0.84	0.64 ± 0.87	0.72 ± 0.92
0.6	"γ"	−0.67 ± 2.33	−0.58 ± 1.89	−0.51 ± 1.58	−0.47 ± 1.36	−0.43 ± 1.19	−0.40 ± 1.06	−0.37 ± 0.95
	"α"	0.32 ± 0.76	0.38 ± 0.78	0.44 ± 0.80	0.51 ± 0.82	0.58 ± 0.85	0.66 ± 0.88	0.74 ± 0.93
0.7	"γ"	−0.77 ± 2.44	−0.67 ± 1.94	−0.59 ± 1.61	−0.54 ± 1.37	−0.49 ± 1.20	−0.46 ± 1.06	−0.43 ± 0.95
	"α"	0.33 ± 0.77	0.39 ± 0.79	0.45 ± 0.81	0.52 ± 0.83	0.59 ± 0.86	0.67 ± 0.90	0.76 ± 0.95
0.8	"γ"	−0.87 ± 2.54	−0.76 ± 2.01	−0.67 ± 1.65	−0.61 ± 1.39	−0.56 ± 1.20	−0.52 ± 1.06	−0.49 ± 0.94
	"α"	0.34 ± 0.78	0.40 ± 0.80	0.46 ± 0.82	0.53 ± 0.85	0.61 ± 0.88	0.69 ± 0.92	0.78 ± 0.98
0.9	"γ"	−0.97 ± 2.64	−0.84 ± 2.06	−0.75 ± 1.67	−0.67 ± 1.40	−0.62 ± 1.20	−0.57 ± 1.05	−0.54 ± 0.93
	"α"	0.34 ± 0.79	0.41 ± 0.81	0.48 ± 0.83	0.55 ± 0.86	0.62 ± 0.90	0.71 ± 0.95	0.81 ± 1.01

VALUES FOR "γ" = γ/c AND "α" = $c\alpha$ FOR SPECIFIED VALUES OF A AND B AND FOR THEIR STANDARD DEVIATIONS IF $n = 1$

A	B	0.30	0.35	0.40	0.45	0.50	0.55	0.60
1.0	"γ"	−1.06 ± 2.73	−0.92 ± 2.12	−0.82 ± 1.70	−0.74 ± 1.41	−0.68 ± 1.20	−0.63 ± 1.04	−0.59 ± 0.92
	"α"	0.35 ± 0.80	0.42 ± 0.82	0.49 ± 0.85	0.56 ± 0.88	0.65 ± 0.93	0.74 ± 0.98	0.84 ± 1.04
1.1	"γ"	−1.15 ± 2.81	−1.00 ± 2.16	−0.88 ± 1.72	−0.80 ± 1.42	−0.73 ± 1.19	−0.68 ± 1.03	−0.64 ± 0.90
	"α"	0.36 ± 0.82	0.43 ± 0.84	0.51 ± 0.87	0.58 ± 0.91	0.67 ± 0.96	0.77 ± 1.02	0.88 ± 1.09
1.2	"γ"	−1.22 ± 2.87	−1.06 ± 2.19	−0.94 ± 1.72	−0.85 ± 1.41	−0.78 ± 1.18	−0.73 ± 1.01	−0.69 ± 0.87
	"α"	0.38 ± 0.84	0.45 ± 0.86	0.53 ± 0.90	0.61 ± 0.94	0.70 ± 0.99	0.81 ± 1.07	0.93 ± 1.16
1.3	"γ"	−1.30 ± 2.91	−1.13 ± 2.20	−1.00 ± 1.72	−0.91 ± 1.40	−0.83 ± 1.16	−0.78 ± 0.98	−0.73 ± 0.83
	"α"	0.39 ± 0.86	0.47 ± 0.89	0.55 ± 0.93	0.64 ± 0.98	0.74 ± 1.04	0.86 ± 1.13	1.00 ± 1.24
1.4	"γ"	−1.36 ± 2.92	−1.18 ± 2.20	−1.05 ± 1.70	−0.95 ± 1.37	−0.87 ± 1.12	−0.82 ± 0.95	−0.77 ± 0.79
	"α"	0.41 ± 0.88	0.49 ± 0.92	0.58 ± 0.96	0.68 ± 1.03	0.79 ± 1.10	0.92 ± 1.21	1.08 ± 1.35
1.5	"γ"	−1.42 ± 2.91	−1.23 ± 2.18	−1.09 ± 1.66	−0.99 ± 1.33	−0.91 ± 1.07	−0.85 ± 0.89	−0.81 ± 0.73
	"α"	0.43 ± 0.91	0.52 ± 0.96	0.61 ± 1.01	0.73 ± 1.09	0.85 ± 1.18	1.01 ± 1.32	1.21 ± 1.53
1.6	"γ"	−1.46 ± 2.87	−1.28 ± 2.13	−1.13 ± 1.61	−1.02 ± 1.27	−0.94 ± 1.00	−0.89 ± 0.82	−0.84 ± 0.65
	"α"	0.46 ± 0.95	0.55 ± 1.01	0.66 ± 1.07	0.78 ± 1.17	0.93 ± 1.29	1.13 ± 1.49	1.38 ± 1.79
1.7	"γ"	−1.50 ± 2.79	−1.31 ± 2.05	−1.16 ± 1.54	−1.05 ± 1.18	−0.97 ± 0.91	−0.91 ± 0.72	−0.88 ± 0.55
	"α"	0.49 ± 0.99	0.59 ± 1.06	0.71 ± 1.15	0.86 ± 1.27	1.04 ± 1.46	1.30 ± 1.76	1.71 ± 2.41
1.8	"γ"	−1.52 ± 2.68	−1.32 ± 1.94	−1.18 ± 1.43	−1.07 ± 1.08	−0.99 ± 0.81	−0.94 ± 0.59	
	"α"	0.53 ± 1.05	0.64 ± 1.13	0.79 ± 1.25	0.97 ± 1.44	1.21 ± 1.74	1.62 ± 2.39	
1.9	"γ"	−1.53 ± 2.53	−1.33 ± 1.80	−1.18 ± 1.29	−1.07 ± 0.94	−1.00 ± 0.65		
	"α"	0.58 ± 1.13	0.71 ± 1.24	0.89 ± 1.42	1.13 ± 1.71	1.53 ± 2.37		
2.0	"γ"	−1.52 ± 2.34	−1.32 ± 1.63	−1.17 ± 1.12	−1.07 ± 0.74			
	"α"	0.64 ± 1.23	0.82 ± 1.41	1.05 ± 1.69	1.44 ± 2.35			
2.1	"γ"	−1.50 ± 2.09	−1.30 ± 1.39	−1.15 ± 0.88				
	"α"	0.74 ± 1.40	0.97 ± 1.68	1.34 ± 2.33				
2.2	"γ"	−1.45 ± 1.78	−1.24 ± 1.08					
	"α"	0.88 ± 1.66	1.25 ± 2.31					
2.3	"γ"	−1.36 ± 1.38						
	"α"	1.16 ± 2.29						

Suppose that we have 20 guinea pigs innoculated with dilutions 1:4, 1:8, 1:16 of a standard toxoid and also of one to be tested against it, that subsequently a dose of the toxin is given, and finally the number of survivors be recorded as follows:[3]

	STANDARD			TO BE TESTED		
DILUTION	n	SURVIVALS		n	SURVIVALS	
1:4	20	20	$P_3 = 1.00$	20	15	$P'_3 = 0.75$
1:8	20	15	$P_2 = 0.75$	20	6	$P'_2 = 0.30$
1:16	20	8	$P_1 = 0.40$	20	1	$P'_1 = 0.05$

From (1) we have $A = 1.30$, $B = 0.60$, $A' = -0.80$, $B' = 0.70$, with $r = 2$ and $\log r = 0.301$.

From the table, entering with $A = 1.30$ and $B = 0.60$, and neglecting for the moment the standard deviations we find "γ" $= -0.73$. Hence from (2) with $ar = 8$ for the middle dilution

$$\log \delta = \log 8 - (-0.73)(0.301) = 0.903 + 0.22 = 1.123, \qquad \delta = 13.3.$$

The 50% end-point is at dilution 1:13.3. For the biological to be tested $A' = -0.80$ is negative which means that "γ" must be positive and equal to 0.44. Hence, still neglecting the standard deviation both in the table and in (2),

$$\log \delta' = \log 8 - (0.44)(0.301) = 0.903 - 0.13 = 0.773, \qquad \delta = 5.9.$$

The strength of the toxoid to be tested is thus only $5.9/13.3 = 0.44$ or 44% of that of the standard at the L.D.50 points.

To discuss the significance of the ratio it is best to test the significance of the differences of the values of $\log \delta$ and $\log \delta'$ as given in (1). The standard deviation of "γ" in the table for $n = 1$ is entered as 0.83 and for "γ'" as 0.77. Dividing by $\sqrt{20}$ since $n = 20$ we have 0.19 and 0.17, respectively. Then multiplying by $\log r$ we find finally

$$\log \delta = 1.123 \pm 0.057, \qquad \log \delta' = 0.773 \pm 0.051$$
$$\text{diff.} = -0.35 \pm \sqrt{(0.057)^2 + (0.051)^2} = -0.35 \pm 0.076.$$

The difference is therefore highly significant.[4]

In comparing these two biologicals the L.D.50 points have been used. If the comparison is to remain valid at other points, the values of α must be nearly enough alike so that the difference between them may be ignored. In this particular case "α" $= 1.00$ and $\alpha =$ "α"$/c = 1.00/0.301 = 3.32$; further, σ("α") $= 0.28$ for $n = 20$ and $\sigma(\alpha) = 0.93$ so that $\alpha = 3.32 \pm 0.93$. The value of α' would not be significantly different from that of α unless it were outside the limits 5.18 and 1.46 which are rather wide open limits. As a matter of fact α' in the illustration is the same as α and the standardization is valid over the whole range.[5]

It sometimes happens that animals are lost during the experiment so that one cannot be sure whether they would have been survivals or not. Suppose, for example, that in the group treated with the standard biological we had had at 1:16 one animal lost, 7 survivors and 12 deaths. If the one lost be taken as surviving we have $\delta = 13.3$ as before, but if it were taken as not surviving we should have $P_1 = 0.35$, $A = 1.2$, $B = 0.65$ which would give "γ" $= -0.66$ and $\delta = 12.7$ which cannot be considered a significant change; but what we know is that $\delta = 12.7$ or 13.3. The change in α would also be well under the sampling allowance; and furthermore the standard deviations whether of γ or α would not be much different on the two different hypotheses.

[1] See these PROCEEDINGS, 29, 79–85, 114–120, 150–154 (1943).

[2] These formulae assume that the numbers are large and may therefore give inaccurate values for the standard deviations when the numbers are as small as they often are in the case of bio-assays; but some estimate of standard deviations seems better than none provided the estimates are used with discretion.

[3] It will be observed that we have used P_3 for the lowest dilution (largest dose) and P_1 for the highest dilution (smallest dose) which is in accord with our previous convention that P_3 represented the greatest effect, which in this case is a protective effect.

[4] If we take the limits specified by the standard deviation itself, we have -0.426 and -0.274 which correspond to ratios of 0.38 and 0.53 in place of the value 0.44; if we should allow twice the standard deviation we should have limits of -0.502 and -0.198 which correspond to ratios of 0.31 and 0.63. We cannot safely assign probabilities of 0.32 and 0.05 for the ratio being outside these respective pairs of limits, but that is always the case with the use of the standard deviation to estimate significance when the true distribution of the ratio of the variable to its standard deviation is unknown.

[5] If two biologicals have a ratio of strength of R when compared at their 50% endpoints, the ratio of strength R_P when compared at any percentage P will be $R_P = Re^Z$, where $Z = 2.65\left(\frac{1}{\text{“}\alpha'''} - \frac{1}{\text{“}\alpha''}\right) \log \frac{P}{Q} \log_{10} r$. For comparison well away from the L.D.50, e^Z may differ considerably from 1 even if "α" and "α''' do not differ significantly.

GROUPS CONTAINING FOUR AND ONLY FOUR NON-INVARIANT SUBGROUPS

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If a group G contains four and only four non-invariant subgroups these subgroups are transformed under G according to a permutation group of degree 4. We shall begin with the case when this permutation group is transitive. It could not be either the symmetric or the alternating group of degree 4 since each of these groups contains more than four non-invariant subgroups and to each of these subgroups there would correspond a non-invariant subgroup of G. This is impossible since G is supposed to contain only four non-invariant subgroups. These subgroups could not be transformed under G according to the octic group because this group itself contains four non-invariant subgroups and these are not transferred transitively under the octic group while the four non-invariant subgroups of G are assumed to be transformed transitively under G. Hence G would have to contain more than four non-invariant subgroups, which is contrary to the hypothesis.

It remains to consider the case when the four conjugate subgroups of G are supposed to be transformed under G according to one of the two regular permutation groups of degree 4 and hence the invariant subgroup of G which corresponds to the identity of this regular group contains the four non-invariant subgroups of G invariantly and is itself either Hamiltonian or abelian. In the former case it could not be the quaternion group since this group does not involve four similar subgroups. Its order could not be a power of 2 since it would then be the direct product of the quaternion group and the abelian group of type 1^m and hence it would involve the abelian group of type 1^{m+1} as a characteristic subgroup.[1] Not all the subgroups of this characteristic subgroup could be invariant under G since the non-invariant subgroups of G are supposed to be conjugate under G. For similar reasons the order of the Hamiltonian group could not be divisible by two distinct prime numbers.

If G would contain exactly four non-invariant subgroups and would transform them according to the non-cyclic regular permutation group of degree 4 then G would involve a subgroup H of index 2 which would have a commutator subgroup of order 2 and an invariant abelian subgroup of index 4 under G. All the operators of H which would not be contained in this abelian subgroup would separately generate the commutator subgroup of H. Since another subgroup of index 2 under G would contain a different commutator subgroup there would be more than four non-invariant sub-

groups in G. This method of proof applies also to the case when the four non-invariant subgroups are supposed to be transformed according to the regular cyclic permutation group of order 4. It therefore results that *when G contains exactly four non-invariant subgroups it must transform them according to an intransitive group.*

It remains to consider the groups which separately contain four and only four non-invariant subgroups such that these subgroups are conjugate in pairs under the group. These subgroups are transformed under G according to an intransive group of degree 4 whose order is either 2 or 4. In the former case G contains an invariant subgroup of index 2 which corresponds to the identity of the group of transformation of its four non-invariant subgroups. As this subgroup contains no non-invariant subgroup it is either abelian or Hamiltonian. In the former case G may be the direct product of a group of prime order and an arbitrary group in the infinite system of groups which is composed of groups which separately involve two and only two non-invariant subgroups. This is obviously the only case in which the order of the abelian subgroup of G which corresponds to the identity in the group of transformation of its four non-invariant subgroups has an order which is divisible by as many as two distinct prime numbers.

When this order is divisible by only one prime number the order of G is a power of 2 and the given abelian subgroup of G which corresponds to the identity in the group of transformations of its four non-invariant subgroups and is of index 2 under G must have exactly three independent generators one of which is of order 2. At least one of the other generators of this invariant subgroup must have an order which exceeds 2 and hence the order of G is at least 32. Each of the four non-invariant subgroups of G may be of order 2. Each of the groups in this infinite system of groups contains a commutator subgroup of order 2 which is generated by its operator of largest order. We therefore arrived at the following theorem: *There are two infinite systems of groups which are separately composed of groups such that each of them contains four and only four non-invariant subgroups which it transforms according to the intransitive group of degree 4 and of order 2. The orders of the groups in one of these systems are a power of 2 while the orders of those in the other system are a power of 2 multiplied by an arbitrary odd prime number.*

It remains to consider the possible groups which separately contain four and only four non-invariant subgroups and transform them according to the intransitive permutation group of degree 4 and of order 4. Such a group G contains two subgroups of index 2 which separately transform each of two non-invariant subgroups into itself and the other two among themselves. These two subgroups have a subgroup of index 4 under G in common which is invariant under G since each of the two given subgroups is invariant under G. Hence G contains also a subgroup of index 2 which transforms

the four non-invariant subgroups in pairs and involves the given invariant subgroup of index 4. This invariant subgroup of index 2 involves no non-invariant subgroup of G and hence it is either abelian or Hamiltonian.

When this subgroup of index 2 is the cyclic group of order 4 then G is the octic group and when it is the cyclic group of order 8 then G is the dicyclic group of order 16. When it is the abelian group of order 8 and of type 2, 1 then G is the group of order 16 obtained by extending this abelian group of order 8 by an operator of order 4 which transforms into their inverses all the operators of this abelian group of order 8 and has for its square an operator of order 2 which is not the commutator of this order. It will be proved that these three groups include all those which satisfy the conditions under consideration. In fact, in such a group the given subgroup of index 2 could clearly not be Hamiltonian. If it is abelian it cannot have more than two independent generators since the remaining operators of the group must transform each of its subgroups into itself. If it is cyclic the remaining operators of the group transform its operators according to one of the three operators of order 2 in its group of isomorphisms. Hence there results the theorem: *There are three and only three groups which separately contain four and only four non-invariant subgroups and transform them according to the intransitive group of degree 4 and of order 4.*

In closing we may direct attention to the fact that if a group G contains five and only five non-invariant subgroups they cannot be transformed under G according to an intransitive permutation group. Such a group could not be a 3, 1 isomorphism between the symmetric group of degree 3 and the group of order 2 since the permutations which are not found in the invariant subgroup of order 3 could not transform the two conjugate subgroups into each other. It could not be the cyclic group of order 6 since the permutation of order 6 could not be non-commutative with each of the non-invariant subgroups of G. As it could also not be the group of order 12 and degree 5 it results that *whenever a group contains five non-invariant subgroups and all its other subgroups are invariant then its non-invariant subgroups appear in a single set of conjugates under the group.*

[1] Cf. G. A. Miller, *Collected Works*, **1**, 266 (1935).

ON INFINITE DIMENSIONAL LINEAR SPACES

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The study of infinite dimensional linear spaces[2] seems to be most fruitful when the spaces considered are more than abstract linear spaces; that is, when further structure has been added by introducing some undefined notion such as a topology, an inner product or a partial ordering. It is the purpose of this note to describe the results of introducing such structure in still another way.

Let us begin by observing that the theory of the classification of abstract linear spaces is quite simple. It is well known that in any linear space there exists a Hamel basis; that is, a set of linearly independent elements whose finite linear combinations constitute the whole space and Löwig[3] has shown that any two Hamel bases for the same space have the same cardinal number. Calling this number the dimension of the space, it is clear that two linear spaces are isomorphic if and only if they have the same dimension and that given any cardinal number there is a linear space with this number as its dimension.

Since most of the commonly studied linear spaces have the same dimension, namely, C, one may, to a large extent, regard the different topological linear spaces, linear lattices, etc., as obtained from a single linear space by introducing different topologies, different partial orderings, etc. This point of view becomes rather suggestive in the case of normed linear spaces because of a theorem of Fichtenholz[4] to the effect that two norms in the same linear space give the same topology if and only if the same linear[5] functionals are continuous with respect to both of them. Thus if X is an abstract linear space of dimension C and X^* is the linear space of linear functionals on X it is clear that there is a natural one-to-one correspondence between an important class of normable topological linear spaces and a certain class of subspaces of X^*.

The method of introducing structure with which this note is concerned is suggested in two different ways by the considerations of the preceding paragraph. First, since each norm topology in X uniquely determines and is uniquely determined by the family of linear functionals which are continuous with respect to it, the structure in X obtained by introducing such a topology is identical with that obtained by *distinguishing a certain subspace of* X^*. Secondly, if one asks what subspaces of an X^* can appear as "norm sets" one is led to seek means of differentiating between subspaces of X^*'s. Although the problem of classifying the subspaces of an abstract linear space is as trivial as that of determining all abstract linear spaces,

this is not the case for the norm set characterization problem. X^* is not merely an abstract linear space but has added structure by virtue of being a space of linear functionals. Furthermore, and this is what is of interest here, this structure may be regarded as induced in X^* by *distinguishing a certain subspace of* X^{**}. In precisely what sense this is true will appear below. If X is any linear space we shall call the result of distinguishing a subspace L of X^* the *linear system* X_L.

It is easy to show that, setting aside a few uninteresting exceptions, for every linear system X_L there is a topology in X with respect to which X is a topological linear space and the continuous linear functionals are precisely the members of L. Hence linear systems are not strictly speaking new mathematical objects and our method of introducing structure is at most a new *method*. However it does lead to a rather unconventional point of view, two features of which we now describe.

We begin with some definitions. Two linear systems X_L and Y_M will be said to be *isomorphic* if there exists an isomorphism T between X and Y as abstract linear spaces such that m is in M if and only if there is an l in L with the property that $m(T(x)) = l(x)$ for all x in X. An isomorphism of a linear system with itself will be called an *automorphism*. If x is a member of a linear space X and L is a subspace of X^* then the member f of L^* such that $f(l) = l(x)$ for all l in X^* will be called the *member of* L^* *associated with* x. In terms of these the following easily proved theorem may be stated. Let X be a linear space and let L and M be subspaces of X^*. Let $X_X{}^*$ be the linear system obtained from X^* by distinguishing those members of X^{**} associated with members of X. Then the linear systems X_L and X_M are isomorphic linear systems if and only if there is an automorphism of the linear system $X_X{}^*$ which carries L into M.

This theorem justifies the statement about the structure of X^* made above and tells us that the problem of classifying the linear systems definable on a fixed linear space is identical with the problem of classifying the subspaces of a certain linear system. Thus methods which occur naturally in one problem may be applied to the other and every definition which we may make differentiating subspaces of systems of the form $X_X{}^*$ carries with it a definition differentiating linear systems and conversely.

The other feature is a natural conjugacy relation that exists between linear systems. If X_L is a linear system one may consider the linear system whose linear space is L and whose distinguished functionals are those associated with members of X. This linear system will be called the *conjugate* of X_L. It is easy to see that a linear system X_L is isomorphic to the conjugate of its conjugate if and only if L is total. Such a linear system will be said to be *regular*. It should be pointed out that the conjugate of the linear system of a normed linear space is not isomorphic to the linear system of the conjugate space unless the normed linear space is reflexive and

the linear system of any normed linear space is regular whether the space is reflexive or not.

The systematic study of linear systems centers around two principal notions each of which is an obvious generalization of a corresponding notion in the theory of normed linear spaces. The first of these is that of closure of a subspace. Let X_L be a linear system. For each subspace M of $X(L)$ let M' denote the set of all l in L (x in X) such that $l(x) = 0$ for all $x(l)$ in M. If M is a subspace of X then M'' will be a subspace of X which contains M. We call it the *closure* of M and call the subspaces of X which coincide with their closures the *closed* subspaces of the system X_L. The family of closed subspaces of a linear system X_L forms a complete lattice under partial ordering by inclusion. The operation $'$ sets up a dual isomorphism between this lattice for X_L and that for its conjugate system. If X_L is regular every finite dimensional subspace of X is closed and the lattice of all closed subspace as an abstract lattice determines X_L up to an isomorphism.[6] The lattice of X_L is modular if and only if whenever M and N are both closed subspaces of X the smallest subspace $M + N$ which contains both M and N is also closed. The notion of disjointness of subspaces of a Banach space introduced by Kober[7] and by Lorch[8] readily generalizes to linear systems and it is possible to prove that the lattice of X_L is modular only if any two closed subspaces with only zero in common are disjoint. Applying these considerations to normed linear spaces using a construction suggested by P. Erdös and S. Kakutani it may be shown that the lattice of closed subspaces of a normed linear space is modular if and only if the space is finite dimensional.

There are several useful facts about automorphisms of linear systems which may be established with the aid of the notion of closed subspace. For example, it is quite easy to show that if X_L is a regular linear system and $x_1, x_2, \ldots x_n$ and $y_1, y_2, \ldots y_n$ are two finite sets of linearly independent members of X then there is an automorphism of X_L carrying each x_i into y_i. Thus in particular the group of automorphisms of X_L is transitive on the non-zero elements of X. It follows also that if M and N are two finite dimensional subspaces of X, then there is an automorphism of X_L carrying M into N if and only if M and N have the same dimension, and that if M and N are closed subspaces of X_L, such that X/M and X/N are finite dimensional, then such an automorphism exists if and only if X/M and X/N have the same dimension. An immediate consequence of this last remark is the following theorem about normed linear spaces. Let X be a normed linear space. Then X has all of the following properties if it has any one of them. (*a*) X is isomorphic to its direct product with a one dimensional normed linear space. (*b*) X is isomorphic to one of its maximal closed subspaces. (*c*) X is isomorphic to its direct product with any finite dimensional normed linear space. (*d*) X is isomorphic to each of its

closed subspaces which has a finite dimensional quotient space. This result suggests that spaces with one and hence all of these "stability" properties might be interesting to study.

The greater part of our results are concerned with our second principal notion, that of boundedness. If X_L is a linear system a subset A of X will be said to be a *bounded* subset of X_L if for each l in L the set of real numbers of the form $l(x)$, where x runs through A, is a bounded set of real numbers. This notion leads at once to a new sort ot closure for subspaces of linear systems of the form X^*_X. Let X be a linear space and let L be a subspace of X^*. The set of all members of X^* which carry bounded subsets of X_L into bounded sets of real numbers is a subspace which contains L. We call it the *bounded closure* of L and denote it by $\bar{L}$. If $L = \bar{L}$ we say that L is *boundedly closed*. It is readily verified that the bounded closure of any subspace is itself boundedly closed. Examples of boundedly closed subspaces of an X^*_X include all closed subspaces, all $\aleph_0$ dimensional subspaces, and all norm sets. It is easy to show that the intersection of any number of boundedly closed subspaces of an X^*_X is again boundedly closed. On the other hand it is not known whether or not the bounded closure of $M + N$ follows from that of M and N. If M is finite dimensional, if M and N are both norm sets or if M is a norm set and N is $\aleph_0$ dimensional then $M + N$ is boundedly closed, but only the last of these theorems is easy. The natural question as to whether or not X is a boundedly closed subspace of $X^{**}_{X^*}$ can be shown to be completely equivalent to a certain problem in measure theory which has been partially solved by Ulam[9]. More particularly, X is a boundedly closed subspace of $X^{**}_{X^*}$ if and only if the dimension $\aleph$ of X is such that any countably additive measure function defined on all subsets of a class of cardinal $\aleph$ taking on only the values 0 and 1 and vanishing at points is identically zero.

Let $\bar{x}$ be a member of the linear system X_L and let $\{x_n\}$ be a sequence of members of X_L. If there exists a sequence of positive real numbers $\{\gamma_n\}$ converging to zero such that $\{(x_n - \bar{x})/\gamma_n\}$ is a bounded subset of X_L we say that $\{x_n\}$ converges to $\bar{x}$. The notion of convergence so defined plays an important role in the discussion of bounded closure. There are several theorems connecting the two notions some of which appear to be indispensable in proving certain theorems about bounded closure alone. By regarding the regular linear system X_L as a subsystem of the linear system L^*_L and considering the closedness of X in L^* with respect to the convergence of sequences, one is led to a notion of completeness for linear systems. If X_L is the linear system of a normed linear space then X_L is complete if and only if the normed linear space is complete and if X_L is an arbitrary regular linear system then X_L is complete if and only if every total subspace of L contains L in its bounded closure.

A classification of subspaces of linear systems of the form X^*_X which in a

sense supplements that given by the notion of bounded closure is suggested by a study of the nature of the boundedness in the linear systems X_L which they define. Let X be a linear space, let L be a subspace of X^* and consider the bounded sets in the linear system X_L. If there is a bounded subset of X_L which is contained in no proper subspace of X we say that L is *relatively bounded*. If there is a countable family of bounded subsets of X_L such that no proper subspace of X contains them all we say that L is *almost relatively bounded*. If for every countable family of bounded subsets $\{B_n\}$ of X_L there is a sequence $\{\gamma_n\}$ of positive real numbers such that $(B_1/\gamma_1)\cup(B_2/\gamma_2)\cup(B_3/\gamma_3)\cup\ldots$ is a bounded subset of X_L we say that L has the *first countability property*. If there exists a countable family of bounded subsets $\{B_n\}$ of X_L such that for every other bounded subset B there is a B_n and a positive real number γ such that B/γ is contained in B_n we say that L has the *second countability property*. If the sequence $\{B_n\}$ in the immediately preceding definition may be replaced by a single bounded set we say that L is *simple*. Every simple L has the other four properties listed above. Moreover there are enough implications between the properties to assure us that of the 32 disjoint classes into which they divide the L's at most eight are not empty. We have examples of L's in seven of these.

There are a number of theorems describing the behavior of L's with various of the above properties. Typical of these are the following. L is relatively bounded if and only if it is contained in a norm set. If L is relatively bounded then there is an automorphism T^* of the linear system X_X^* such that $L\cap T^*(L) = 0$. If L has the first countability property then every maximal subspace of L also has the first countability property.

Let X_L be a linear system. We say that a subset A of X is *uniformly bounded* if for each bounded subset B of the conjugate system $\text{l.u.b.}_{(l\,\epsilon\,B)}(\text{l.u.b.}_{(x\,\epsilon\,A)}l(x)) < \infty$. There always exists a subspace M of X^* such that the uniformly bounded subsets of X_L are identical with the bounded subsets of X_M. M is not unique but our proof of its existence leads to a unique result which we call the *reach* of L. If every bounded subset of X_L is uniformly bounded we say that X_L is a *uniform linear system* and that L is *uniform*. It is not known whether or not the bounded closure of a uniform L is uniform, nor whether or not the operation of taking the reach is idempotent. Among the things that may be said about uniformity are the following. Every complete linear system is uniform. The linear system of a normed linear space X need not be uniform but will be if X is of the second category or is such that X^c/X is finite dimensional where X^c denotes the completion of X. Every relatively bounded uniform linear system is simple.

By making use of the general theory of linear systems one can obtain information about the nature of norm sets. In doing this it is convenient to introduce a concept slightly more general than that of norm set. A real

valued function defined on a linear space which has all of the properties of a norm except that it may be zero at non-zero elements of the space we call a *pseudo-norm*.[10] The set of all linear functionals continuous with respect to a pseudo-norm we call a pseudo-norm set. A pseudo-norm set is a norm set if and only if it is total. Among our theorems on pseudo-norm sets are the following. If $L_1, L_2, \ldots$ is a sequence of pseudo-norm sets then $L = L_1 \dot{+} L_2 \dot{+} \ldots$ is bounded closed but is a pseudo-norm set if and only if for some n, $L = L_1 \dot{+} L_2 \dot{+} \ldots \dot{+} L_n$. The intersection of a finite number of pseudo-norm sets is again a pseudo-norm set and if the underlying linear space is infinite dimensional, any pseudo-norm set is the intersection of two norm sets. A subspace of an X^* is an intersection of pseudo-norm sets if and only if it is relatively bounded and boundedly closed. Such a subspace need not be a pseudo-norm set. On the other hand if X_L is a complete regular linear system then L is a norm set if and only if it is relatively bounded and boundedly closed. The dual of the above theorem on sequences of pseudo norm sets is not true. However, by using uniform boundedness a notion of *regular inclusion* may be introduced in terms of which the following true analog may be stated. If L_0 is a total subspace of an X^* and $L_1, L_2, \ldots$ is a sequence of norm sets each of which contain L_0 regularly then $L = L_1 \bigcap L_2 \bigcap \ldots$ is a norm set if and only if for some n, $L = L_1 \bigcap L_2 \bigcap \ldots \bigcap L_n$.

In a subsequent note we shall describe the results we have obtained by applying the theory of linear systems to the study of convex topological linear spaces. The proofs of the theorems announced in these notes as well as those of a good many others will appear in two longer papers to be published later.

[1] This note is a highly condensed résumé of the major portion of the author's doctoral thesis, Harvard, 1942.

[2] By a linear space we mean a real linear space. See Banach, *Théorie des opérations linéaires*, 1932, p. 26.

[3] Löwig, H., "Über die Dimension linearer Räume," *Studia Mathematica*, **5**, 18–23 (1934).

[4] Fichtenholz, G., "Sur les fonctionelles linéaires, continues au sens généralisé," *Rec. Math. (Mat. Sbornik) N. S.*, **4**, 192–213 (1938).

[5] In this note linear means additive and homogeneous.

[6] Cf. Mackey, G. W., "Isomorphisms of Normed Linear Spaces," *Ann. Math.*, **43**, 244–260 (1942).

[7] Kober, "A Theorem on Banach Spaces," *Compositio Mathematica*, **7**, 135–140 (1939).

[8] Lorch, E. R., "On a Calculus of Operators in Reflexive Vector Spaces," *Trans. Amer. Math. Soc.*, **45**, 217–234 (1939).

[9] Ulam, S., "Zur Masstheorie in der allgemeinen Mengenlehre," *Fund. Math.*, **16**, Satz 1 146 (1930).

[10] Not to be confused with the pseudo-norm of Hyers; Hyers, D. H., "A Note on Linear Topological Spaces," *Bull. Amer. Math. Soc.*, **44**, 76–80 (1938). Cf., however, Wehausen, J. V., "Transformations in Linear Topological Spaces," *Duke Math. Jour.*, **4**, 157–169 (1938), where the term is used in our sense.

ON CERTAIN NON-LINEAR DIFFERENTIAL EQUATIONS OF THE SECOND ORDER

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The qualitative nature of the solutions of second order non-linear differential equations with a periodic forcing term is still largely an open matter. Here we shall state certain results we have succeeded in demonstrating for a class, C, of such equations of considerable importance in applied mathematics. Rather than define the Class C here, we indicate the nature of C by stating that included in C as a subclass are the equations

$$\ddot{x} + f(x)\,\dot{x} + g(x) = e(t)$$

where (1) $f(x)$, $g(x)$ and $e(t)$ are analytic functions for real values of x and t, respectively; (2) there exists some $a > 0$ such that $f(x) \geqq a$; (3) $xg(x) > 0$ for large $|x|$, and $|g(x)| \to \infty$ as $|x| \to \infty$; (4) there exists some $b > 0$ such that for large $x > 0$, $g(\xi) > bg(x)$, $\frac{1}{2}x < \xi < x$; and (5) $e(t)$ has period L. (L we assume is the smallest period of $e(t)$.)

It is known that an equation of class C possesses at least one solution of period L.

Our results state that each equation of Class C falls into one of four exhaustive and mutually exclusive cases according to the qualitative behavior of its solutions as $t \to +\infty$. We now list for each case a necessary and sufficient condition to assure that an equation of Class C falls under that case and then give some further properties of the case.

Case I.—A necessary and sufficient condition for Case I is that the equation have more than one solution of period L.

Further properties of Case I:

(a) There are an odd number, $2n + 1$, of solutions of period L of which $n + 1$ are stable and n are unstable as $t \to +\infty$.

(b) All solutions, other than the n unstable ones of period L, tend to one of the $n + 1$ stable solutions of period L as $t \to +\infty$.

Case II.—A necessary and sufficient condition for Case II is that there exist at least one periodic solution of least period qL, q an integer > 1. (Such a solution is called subharmonic.)

Further properties of Case II:

(a) There exist no subharmonics with period distinct from qL.

(b) The one solution of period L is stable if $q > 2$.

(c) There are an even number of subharmonic solutions, half of which are stable and the other half unstable.

(*d*) All solutions, other than the several unstable subharmonic ones, tend to the stable subharmonic ones or to the solution of period L as $t \to +\infty$.

Case III.—A necessary and sufficient condition for Case III is that there exists only one periodic solution and that all other solutions tend to this one as $t \to +\infty$.

Case IV.—A necessary and sufficient condition for Case IV is that there exist only one periodic solution and that not all solutions tend to this one as $t \to +\infty$.

Further properties of Case IV:

(*a*) The periodic solution is stable.

(*b*) There are solutions which are of the type Birkhoff calls discontinuous recurrent.

We observe that any equation of Class *C* which has more than one periodic solution falls under Case I or Case II. Cases I, II and III are all known in practice. What conditions are required to exclude the possibility of Case IV, which we shall term the singular case, may be a hard question to answer. Case IV is intimately related to the singular case for motion on a torus.